



The Challenge of Establishing the Burden of Anaphylaxis: Some Recent Trends

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Abstract

Purpose of review This review aims to describe some of the limitations in defining anaphylaxis and therefore the difficulties in studying its epidemiology. Despite these limitations we also aim to describe some of the trends observed in recent studies.

Recent findings The epidemiological study of anaphylaxis is problematic. Although first described over 100 years ago, the definition of anaphylaxis has undergone revision in the last 2 decades, and a new international consensus definition was proposed in 2014. Clinical diagnostic criteria have been in use for little over a decade. Mast cell tryptase can be used to confirm the diagnosis, but is not always available, is of little use in determining immediate treatment and is not performed in many cases of suspected anaphylaxis. Epidemiological studies rely on clinical diagnosis and medical coding systems which have many limitations.

Summary Recent changes adopted in the ICD-11 will aid the detection and classification of anaphylaxis cases. The absence of an objective gold standard and the difficulty in data quality at a population level mean that reliable epidemiologic data are difficult to obtain. Anaphylaxis seems to be increasing, with food-induced case in paediatrics and drug-induced cases in adults the main drivers.

Introduction

The term anaphylaxis was first used by Richet and Portier [1] to describe the clinical reaction observed in dogs subjected to repeated injection with venom isolated from the sea anemone *Actinia equina*. Initially, the extreme reaction observed was attributed to the absence or reduction of a protective factor ("anaphylaxis" derived from Greek roots ana "against" and phylaxis "protection"); however, subsequent research confirmed the opposite, the provocation of an exaggerated hypersensitivity reaction.

After more than 100 years of research, in which various biochemical pathways have been identified along with potential biochemical markers, tests for subsequent allergen identification and a treatment in injectable

adrenaline (epinephrine), the diagnosis remains based on clinical criteria [2]. The absence of reliable biomarkers or reference standards makes confirming the diagnosis difficult. The majority of cases will be seen initially by emergency physicians and not allergy specialists, and as such quantifying the disease burden is difficult. Even with these problems, recent evidence suggests a rising incidence.

This review aims to describe some of the limitations in defining anaphylaxis and therefore the difficulties in studying its epidemiology. Despite these limitations we also aim to describe some of the trends observed in recent studies.

What is anaphylaxis?

Anaphylaxis has been defined in a variety of manners [3–5] (Table 1); however, consensus definitions tend to refer to "a serious, generalized or systemic allergic or hypersensitivity reaction that can be life threatening or fatal." [6]. Consensus guidance also suggests that terms such as shock or anaphylactic shock should be avoided, because shock is not obligatory criteria for the diagnosis of anaphylaxis [2] (Table 2). Terms such as "anaphylactoid reaction" and "pseudo-anaphylaxis" should also be referred to as anaphylaxis [6, 7] reflecting their often identical clinical severity (and initial treatment) which may have been previously underestimated due to physician and/or patient perception of the old nomenclature.

Diagnostic criteria were specifically designed by consensus to be as sensitive as possible with an aim to detect at least 95% of cases of potential anaphylaxis. As stated previously, shock is not obligatory allowing diagnosis and treatment before cardiovascular collapse; for example, patients with comparatively "mild"

Table 1. Definitions of anaphylaxis by international organization

WAO guidelines	AAAAI/ACAAI guidelines	EAACI guidelines
"A serious life-threatening generalized or systemic hypersensitivity reaction"	"An acute life-threatening systemic reaction with varied mechanisms, clinical presentations and severity that results from the sudden release of mediators from mast cells and basophils"	"A severe life-threatening generalized or systemic hypersensitivity reaction"
"A serious allergic reaction that is rapid in onset and might cause death"		
WAO, World Allergy Organization AAAAI, American Academy of Allergy, Asthma and Immunology ACAAI, American College of Allergy, Asthma and Immunology EAACI, European Academy of Allergy and Clinical Immunology		

Table 2. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g. generalized hives, pruritus or flushing, swollen lips, tongue or uvula)

and at least one of the following:

- a. Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia)
- b. Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (e.g. generalized hives, itch-flush, swollen lips, tongue or uvula)
 - b. Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia)
 - c. Reduced BP or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
 - a. Infants and children, low systolic BP (age specific) or greater than 30% decrease in systolic BP*
 - b. Adults, systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; BP, blood pressure

*Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2× age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years

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symptoms such as urticaria and vomiting meet diagnostic criteria, and this may encourage early treatment with intramuscular adrenaline.

These criteria underwent validation both retrospectively [8] and prospectively [9] in both cases using expert opinion from two allergy specialists as the reference standard for anaphylaxis diagnosis. Retrospective validation showed a sensitivity of 96.7% and a specificity of 82.4% (positive likelihood ratio (LR), 5.48; and negative LR, 0.04), with a Kappa statistic of 0.77 for inter-rater agreement between the two allergy specialists. Prospective validation also showed a high sensitivity of 95.1% and a specificity of 70.8% (positive LR, 3.26; negative LR, 0.07), in this case with a Kappa statistic of 0.7.

Whilst this evidence suggests that the (absence of) criteria will have a high negative predictive value, the process of validation highlights the difficulty in case identification in anaphylaxis. In the absence of a true objective reference standard, the comparison made was between 2 sources of level V evidence (criteria based on consensus statement vs expert opinion). There was discordance between the two allergist-immunologists in 10% of cases retrospectively [8] and 16% prospectively [9], as a further confounding factor the allergy specialists were familiar with the diagnostic criteria. There has been great difficulty in establishing a subjective reference standard.

Pathophysiology of anaphylaxis

The clinical criteria were proposed to be more sensitive than specific and evidence suggests that this is the case. They identify the clinical

condition produced by end effectors of anaphylaxis, specifically the release of tryptase and histamine amongst other inflammatory mediators [10••, 11••]. In classical “type I” anaphylaxis sensitization and production of allergen specific, IgE by B cells leads to IgE-mediated activation and degranulation of mast cells and basophils.

The majority of cases of anaphylaxis are thought to be IgE mediated; however, certain agents such as chemotherapy and monoclonal antibodies can produce clinical findings that meet anaphylaxis diagnostic criteria through other pathways. These agents may be able to stimulate the release of cytokines such as TNF- α , IL-6 and IL-1 β from T-Cells, macrophages and monocytes in so called “cytokine release reactions (CRR)” or mixed (type I plus CRR) [10••, 12, 13]. Histamine and tryptase release can also be stimulated directly by the action of complement, a mechanism thought to be involved in anaphylaxis reactions to contrast dyes, glycosaminoglycans and dialysis membranes [10••, 14]. The mainstay of treatment continues to be early identification and intramuscular adrenaline administration; therefore, wide reaching clinical diagnostic criteria seem appropriate for the diagnosis of these reactions.

The clinical phenotype of type I anaphylaxis can also be induced through non-IgE-mediated pathways. Direct activation of mast cells may result from stimulation of the human G protein-coupled receptor MRGPRX2 [10••, 15, 16]. This protein can act as a receptor for several types of medications (including neuromuscular blocking agents, fluoroquinolones and vancomycin), potentially accounting for a significant proportion of anaphylaxis related to these agents. Furthermore, murine models have suggested a potential role for IgG in IgE-independent anaphylaxis [17, 18], a subject for further research in humans.

The typical clinical presentation and triggers of anaphylaxis vary by age [19–27]. In young children food induced anaphylaxis (FIA) is more frequent [28], before being overtaken by drug induced anaphylaxis (DIA) and hymenoptera venom induced anaphylaxis in adolescence and adulthood. Young children manifest the disease in different ways, they typically have fewer cardiovascular manifestations [21, 27, 28] and a lower mortality rate [29–32]. Children also typically have lower levels of serum tryptase (as a marker of mast cell activation) [33], having typically FIA which itself is associated with lower serum tryptase levels [34, 35].

These differing phenotypes and endotypes by age and trigger (which in themselves are co-related) suggest that under the umbrella term “anaphylaxis”, there are several potentially different disease entities. Initial treatment is similar; however, further recognition of the endotype may permit better subsequent care in the age of precision and patient tailored care [14, 36].

Can biomarkers help understand the epidemiology of anaphylaxis?

Although anaphylaxis is a clinical diagnosis, the current gold standard laboratory test is serum total mast cell tryptase (MCT), which is released

upon degranulation of mast cells during anaphylaxis. MCT is released minutes after exposure, rising to a peak at around 90–120 min, and has a $T_{1/2}$ of around 2 h [37••]. Peak levels are correlated with the severity of episode and are higher in DIA and hymenoptera stings as opposed to FIA, possibly due to a more localized activation of mast cells.

An elevated level above around 9–11 $\mu\text{g/L}$ (depending on assay) is diagnostic [38, 39], however, has reported sensitivities of around 55–64% [37••] and performs worse in light to moderate reactions. Repeat sampling for baseline after resolution of the episode (often performed weeks later) and considering a raise to “ $>(1.2 \times \text{Baseline}) + 2 \mu\text{g/L}$ ” as positive can increase the sensitivity to >80% even in paediatric anaphylaxis [40].

In clinical practice, the MCT is of little use in the acute setting; however, when there is diagnostic uncertainty, a positive value (or elevation compared with baseline) can confirm anaphylaxis and guide further investigation or avoidance strategies.

Direct measurement of histamine is impractical; it has a half-life of 15 min and is unstable *ex vivo*, needing either immediate analysis or freezing. There are however a series of novel biomarkers in study.

Chymase is a serine protease mostly found in mast cell granules. It has a longer half-life than MCT, remaining elevated at least 24 h after anaphylaxis [37••, 41]; further study is required to establish its performance as a diagnostic test. In patients that underwent allergy tests for suspected drug allergies, carboxypeptidase A3 (CPA3) (another mediator of anaphylaxis released by mast cells) was found to be positive in saliva following a positive challenge [42]. CPA3 and MCT are not strongly correlated. Elevations of CPA3 in serum and saliva in cases of suspected anaphylaxis, including patients with a negative MCT, have been described [43, 44].

Whilst there has been a focus on markers of mast cell activity, there are some basophilic mediators being studied at the moment. Chemokine (C–C motif) ligand 2 (CCL2) is a major basophil chemotactic factor, which has been purported to have a sensitivity and specificity of 94 and 96%, respectively [45]. Recent work also suggests a correlation with severity of reaction [46]. However, CCL2 levels return to baseline around 2 h after the episode. Basogranulin has also been described as a marker of basophil function; however, its serum levels are apparently only fleetingly elevated [47].

Other potential biomarkers and mediators also have various limitations [37••]. Platelet activating factor (PAF) is raised in anaphylaxis but has a half-life of less than 5 min. Dipeptidyl peptidase I (DPPI) is non-specific biomarker of uncertain utility in anaphylaxis. Although urinary N-methyl histamine is correlated with plasma histamine, measurement usually requires a 24-h urine sample.

Unfortunately, the perfect biomarker does not exist. One potential direction for the future may be panel arrays testing several biomarkers simultaneously. Laboratory turnaround time and sensitivity would have to be markedly improved to have clinical impact. An idealized “perfect” device might be similar to measuring capillary blood glucose, a point of care test giving an immediate response. This would certainly revolutionize the identification and treatment of

anaphylaxis (along with its epidemiological study); however, at this point in time, such a device is only a proverbial pipe dream.

How is anaphylaxis being measured at a population level?

To calculate meaningful epidemiological measures, it is necessary to define the numerator (number of cases) and the denominator (population at risk). In anaphylaxis there are obvious difficulties in determining the numerator, with problems of case definitions, a heterogeneous disease entity and the necessity to maintain a broad clinical definition to promote early treatment. There are also difficulties in sampling the denominator, with a reduction in data quality when case definitions at a population level are used (as discussed below). Similar to Heisenberg's uncertainty principle, it seems the numerator and the denominator cannot be accurately studied at the same time. Studies that focus on accurately diagnosing anaphylaxis cannot guarantee that they include the whole at risk population, and studies that use national databases are limited by their case definitions.

Recent national-level population studies [20, 23•, 29, 31, 32•, 48, 49] have used data based on codification systems such as the International Classification of Disease (ICD) codes. If there is obligatory notification as opposed to passive, and if the data comes from a reliable national database, then theoretically, all the cases should be counted, and the population data can provide the denominator. Such a database could give the rate of anaphylaxis for that population (as opposed to an estimate based on a population sample).

To give accurate information, the cases have to be correctly identified. The majority of cases of anaphylaxis will be seen in the emergency department, so correct coding depends on the medic recognizing the symptoms and knowing the correct code. Previous iterations of ICD codes have had limited options for codification of anaphylaxis (Table 3); however, the most recent iteration, ICD-11 has undergone extensive research to facilitate and improve the coding of anaphylaxis [50•, 51, 52, 53••].

ICD-9 had 3 codes that specifically mentioned anaphylactic shock: anaphylactic shock to food, anaphylactic shock to serum or anaphylactic shock unspecified. The term "shock" is included in ICD-9, whilst it is not obligatory criteria of the clinical diagnosis. Previous retrospective validations of ICD-9 have shown poor positive predictive values, even for the code 995 "anaphylactic shock" with PPVs of around 50–55% [54, 55]. Sensitivity is probably also low with one study reporting that anaphylaxis specific codes only captured 42% of total cases of anaphylaxis [56]; in this study, further cases were identified using other ICD-9 codes, and medical records were reviewed and compared with the anaphylaxis clinical criteria [2].

The 10th iteration of ICD included new codes anaphylaxis triggers that were not included in ICD-9 (Table 3) however maintains "shock" as part of the terminology. This may continue to cause doctors to try and code episodes of anaphylaxis under other symptom specific codes, which may lead to under reporting [53••], with one single-centre study suggesting that paediatric anaphylaxis in their centre was coded under a non-anaphylaxis code in 87.5% of cases [57].

Table 3. Comparison of anaphylaxis codes by ICD iteration

Chapter headings: ICD-9—Injury and poisoning ICD-10—Injury, poisoning and certain other consequences of external causes			
ICD-9-CM	Descriptor	ICD-10-CM	ICD 11: Chapter 4—Disorders of the immune system
995.0	Anaphylactic shock, unspecified	T78.2XX	4B50 Anaphylaxis due to allergic reaction to food
995.6	Anaphylactic shock or reaction due to unspecified food	T78.0XX	4B51 Drug-induced anaphylaxis
995.60–995.69	Codes for specified foods, e.g. 995.61/T78.01XX—peanuts	T78.01XX–T78.09XX	4B52 Anaphylaxis due to insect venom
999.4	Anaphylactic shock to serum	T80.5XX	4B53 Anaphylaxis provoked by physical factors
No specific code in ICD-9-CM	Anaphylactic shock to drug	T88.6XX	4B53.1 Exercise-induced anaphylaxis
	Anaphylaxis to food additives	T59.1XX	4B53.2 Cold-induced anaphylaxis
	Anaphylaxis to immunizations	T88.1XX	4B53.Y Anaphylaxis provoked by other specified physical factors
Examples of potentially Anaphylaxis related codes			4B53.Z Anaphylaxis provoked by unspecified physical factors
989.5	Toxic effect of venom or other arthropods	T63.43XX	4B54 Anaphylaxis due to inhaled allergens
995.1	Angioneurotic oedema	T78.3XX	4B55 Anaphylaxis due to contact with allergens
995.4	Shock caused by anaesthesia	T88.2XX	4B56 Anaphylaxis secondary to mast cell disorder
708.0	Allergic urticaria	L50.0XX	4B5Y Other specified anaphylaxis
708.9	Urticaria unspecified	L50.9XX	4B5Z Anaphylaxis, unspecified

Mortality data can be a powerful source of epidemiological information, and in many countries, obligatory reporting ensures a near 100% registry of cause of death by ICD code. Anaphylaxis codes from ICD-10 could not be considered underlying causes of death. A retrospective review of a Brazilian registry identified 498 deaths related to anaphylaxis over a 2-year period. Seventy-five percent were defined as definitely related to anaphylaxis, where a specific anaphylaxis code had been registered as a contributing factor. Twenty-five percent were deemed “possible” anaphylaxis deaths on manual review and had not been coded with any anaphylaxis code, for example, laryngeal spasm secondary to contact with wasps [58]. Including these additional possible anaphylaxis deaths increases the estimation of anaphylaxis mortality from 0.65 to 0.87 per million per year.

The inadequacy of ICD-9 and ICD-10 for coding anaphylaxis and allergic disease, as well as the fact that anaphylaxis was coded under the injury and poisoning headings, leads to calls for a revamp of codes for the new ICD-11. The allergy community was surveyed [59], and new codes were developed by “crowdsourcing” [52], with consultation by allergy specialists from around the world, as well as advice from members of the ICD topic advisory groups and the World Health Organization [60].

The new ICD-11 codes include a new chapter heading “Disorders of the immune system” and a new hierarchical arrangement allowing better

codification of anaphylaxis. In a study performed by the Allergy in ICD-11 development group showed that the ICD-11 codes had higher inter-rater reliability for classification of anaphylaxis from hospital records between 2 professional coders [61•]. ICD-11 showed correspondence in 71.5% of codes (Cohen's Kappa 0.77) compared with 52.4% correspondence (Cohen's Kappa 0.63) for ICD-10.

Reanalysis of the Brazilian mortality database [58] using the new ICD-11 codes [62] resulted in a total of 639 deaths being attributed to anaphylaxis, with 95% defined as "definitive anaphylaxis deaths". Using these values would give a mortality rate of 1.12/million/year, compared with 0.65/million/year obtained by only using deaths with an ICD-10 anaphylaxis code as a contributing factor. This evidence was presented to the WHO mortality reference group, which altered coding rules for ICD-11 to allow the addition of allergic conditions, including anaphylaxis, as underlying causes of deaths in official mortality statistics [50•].

The transition from ICD-10 to ICD-11 will start from 2022, and performance of the new codes will need to be prospectively validated in a variety of settings. There will also be the challenge of effectively comparing between the two coding periods. The new ICD-11 codes seem to reduce the risk of underestimating the burden of anaphylaxis; however, in a billing/discharge setting, they will still at times rely on adequate identification of clinical anaphylaxis by the attending physician.

Important trends in anaphylaxis for further study

Although many limitations of the current literature are discussed above in this review, there are still some recent trends that can be identified. The estimations of incidence and/or prevalence may be more influenced by case definitions, and population data may be incomplete, but if the biasing factors are equal across time, then temporal trends identified may be reliable. Table 4 identifies some recent population level studies that have attempted to respond to the need for better epidemiological data.

General upward trend in cases of anaphylaxis

Several large population-based studies from around the 2000s to 2010s have all shown an increase in rates of anaphylaxis [23•, 26, 29–32•, 48, 49, 63–69]. These studies include information from the UK, the USA, Canada, Australia, Denmark, Sweden, Korea and Taiwan (Table 4). Interestingly two of the larger population studies in the USA [23•] and the UK [32•], both based on ICD-10 codes and large national databases, suggest a possible plateau after 2010 and even a slight decrease.

Large population studies from the UK [32•], the USA [29] and Denmark [49] have suggested that this increase in incidence has not translated to an increased mortality in these populations, with one study from Canada [69] describing a decrease. This is in contrast to some other studies suggesting that mortality has in fact increased in Australia [31] and the USA [30]. A recent review showed that whilst there was an absolute mortality increase related to increases in FIA [31], the study also showed a falling mortality per case

Table 4. Characteristics of recent population based epidemiologic studies on anaphylaxis

Study	Area	Period	Data sources	Definition	No. cases	Population	Increase in rate	Trends
Mullins et al. [63] 2015	Australia	1998/99–2011/12 (14 years)	National Hospital Morbidity Database	ICD-10	IA 33622	18.7million in 1998 22.3million in 2011	IA 6.3 to 17.7 per 100,000 person-years	Increase in admissions
Jeppesen et al. [49] 2015	Denmark	1995–2012	Obligatory National Database	ICD-10	Deaths 50 IA 6707	7 million population (103 million person-years)	IA 4.1 to 10.6 per 100,000 person-years	Increase in admissions, mortality stable
Turner et al. [32] 2015	England and Wales	1992–2012	Obligatory national databases for admissions and fatalities, Prospective fatal anaphylaxis registry	ICD-9 ICD-10	Deaths 480 IA 25524	52–54 million***	Mortality 0.47 per million per year IA 1 to 7 per 100,000 person-years	Increase in admissions, mortality stable
Kivistö et al. [48] 2016	Finland and Sweden	Sweden 1999–2011	Obligatory National Database	ICD-10	IA 11336	IA Finland 1987 Sweden 5433	Paediatric Population Finland 1.25 million Sweden 2.15 million	Paediatric IA: Finland 7.8 to 15.8 per 100,000 person-years, Sweden 13.7 to 31.8 per 100,000 person-years
Increase in paediatric admissions								
Yang et al. [64] 2017	Korea	2008–2014	National Health Insurance Database	ICD-10	Episodes 75918	50 million (97.9% of population)	16.02 to 32.19 per 100,000 person-years	Increase in episodes
Jeong et al. [65] 2018	Korea	2010–2014	National Health Insurance Database	ICD-10**	Episodes 65095	50 million (97.9% of population)	20.55 to 35.33 per 100,000 person-years	Increase in episodes
Tejedor-Alonso et al. 2015 [66]	Spain	1998–2011	National Hospital Admissions Database	ICD-9	IA 11336	40–47million***	IA: 1.35 to 2.38 per 100,000 person-years	Increase in admission
Yao et al. [67] 2018	Taiwan	2001–2013	National Insurance Database	ICD-9	ACPS 2496 IA 495 (excl. ICU)	34.4 million person-years	APCS 4.79 to 8.20 per 100,000 person-years IA 1.43 to 1.51 per 100,000 person-years (NS), ITU 0.49 to 0.81 per 100,000 person-years	Increase in episodes and ICU admissions
Lee et al. [26] 2016	USA	2001–2010	Record linkage system	ICD-9-CM Case note review	ED 631	1.5 million	person-years*	ED 42 per 100,000 person-years (average) (Min 19.1, max 57.2)
Increase in ED attendance								
Jerschow et al. [30] 2014	USA	1999–2010	Nationwide mortality database, Census population data	ICD-10-CM	Deaths 2458 (Deaths 3051**)	280–300 million	Mortality average 0.69 per million per year (0.86 per million**)	Increase in fatal DIA, Increase in fatal FIA in African-Americans

Table 4. (Continued)

Study	Area	Period	Data sources	Definition	No. cases	Population	Increase in rate	Trends
Ma et al. [29] 2014	USA	1999–2009	3 nationwide databases	ICD-9-CM Hospital data, ICD-10-CM Mortality data	Deaths 2229 IA 71613 ED 78623 (4 year period)	280–305 million population*	Mortality 0.63 to 0.76 per million per year IA 2.11 to 2.5 per 100,000 (person-years) ED 5.9 to 7.1 per 100,000 (person-years) Outcome as percentage of episodes: Admission 17.6%, ICU 5.3%, Intubation 1.4% APCS 153 to 218 per 100,000 person-years IA 2.3% of anaphylaxis cases IA 3.5 to 5 per 100,000 person-years*	Increase in mortality, IA and ED attendance
Motosue et al. [68] 2017	USA	2005–2014	Nationwide Insurance Database	ICD-9-CM	ED 56,262 IA: 9881 ICU 3000 Intubation 810	100 million "enrolees"		Increase in admission and intubation
Chaaban et al. [23] 2019	USA	2004–2016	Nationwide Insurance Database	ICD-9-CM ICD-10-CM	APCS episodes 462,906	217 million person-years		Increase in APCS Plateau and decrease Increase in LOS

Rates converted to the same unit where possible

APCS, all patient care settings; IA, inpatient admission; ED, emergency department; ICU, intensive care unit; NS, not significant; LOS, length of stay

*Calculated from information available, **Algorithm based on ICD codes to find under classified cases, ***Verified from sources given in article

[70•]. These studies mostly used ICD-9 and 10 codes for mortality data which may underestimate anaphylaxis deaths.

Increasing prevalence of FIA in the paediatric age

FIA is the principal cause of anaphylaxis in the paediatric age range, and almost all studies point to an increasing rate of FIA and paediatric anaphylaxis [23•, 26, 32•, 49, 63–66, 68]. Whether the paediatric age range that carries the highest burden remains unclear, yet several studies describe children and adolescents as having the highest rate of anaphylaxis [23, 32, 63], particularly under 5 years old.

The paediatric age range nevertheless has had the highest rate of increase in anaphylaxis cases [23•, 26, 32•, 63, 65, 66, 68] with one study even reporting a 10-fold increase across a 17 year period [49]. Thankfully paediatric mortality from anaphylaxis and FIA remains low [30, 49] and has not risen with the increase in incidence of FIA [23, 32]. Mortality from FIA starts to increase during the 2nd to 3rd decades of life but is still an infrequent cause.

Few of the studies mentioned in Table 4 codified FIA by trigger, and other types of studies may be more appropriate for accurately identifying allergens (such as children followed up by allergy specialists). In one large US study [23•], the most common triggers specified were peanut, nut/seed and then fish; each trigger increased in proportion during the study period whilst “food unspecified” decreased. The UK triggers [32•] were similar: peanuts and nut/seed; however, milk was the third most frequent trigger at the end of the study period. In an Australian mortality study [31], seafood was implicated in 50% of FIA deaths.

Whilst there is substantial evidence for increasing anaphylaxis from around the globe, the cause for this trend has not been established. Differing weaning strategies may influence future rates of food allergies [71], whereas increasing globalization means a greater availability of ingredients and dishes that may contain hidden allergens [72], either that may not be recognized by the patient or allergens that have a degree of cross reactivity. To further confuse the matter, one recent study [73] using National Health and Nutrition Examination Survey (NHANES) cohorts showed no difference in sensitization (food-specific IgE measured by ImmunoCAP) between cohorts of children over the last 2 decades, contrary to what may have been expected by the increase in FIA.

Increasing prevalence of DIA in adults

With many west countries having an ageing population, along with the demographic phenomenon of the “baby-boomer” generation, rates of polypharmacy have been increasing [70•]. It is therefore unsurprising that several studies show DIA in adults as the most frequent cause of anaphylaxis [26, 49, 64, 65], and the literature suggests a rising frequency. There may be some issues around coding which should improve with ICD-11, for example, Chaaban et al. report a 15-fold increase in DIA in 1 year, which corresponds to the change from ICD-9 to ICD-10 in their study [23•].

Evidence from USA [30] would suggest an increasing rate of DIA anaphylaxis deaths. The main drugs implicated in fatal DIA with ICD-10 codes for

anaphylaxis were antibiotics (41%), radiocontrast (30%) and antineoplastic drugs (12%). The same study also identified a further 306 cases of fatal DIA by using an ICD code search algorithm. In these cases the drugs implicated were antihypertensives (26%), anaesthetics (18%) and NSAIDs (14%). The differing culprit agents may represent coding or recognition errors for DIA provoked by these medications.

By and large, these triggers are similar to what has been described in the literature at hospital level, with antibiotics as the major cause [74]. A recent single-centre study from Korea [75] found antineoplastics as main cause of in-hospital anaphylaxis (42%), specifically cisplatin, followed taxanes and monoclonal antibodies. Radiocontrast media were responsible in 32.2%, with the next most important agents' beta-lactam antibiotics and neuromuscular blocking agents (mainly rocuronium).

The risk of DIA seems to increase with age and may be multifactorial [70•], perhaps related to alterations in immune function with age or polypharmacy. With an ageing population, and more people living longer and healthier, a greater proportion of older patients will be subjected to diagnostic imaging and surgical interventions and thus will have more exposition to these triggers. Early detection and prevention will continue to be important in the future.

Anaphylaxis to hymenoptera venom

The rates of anaphylaxis to insect venom have remained relatively stable [31, 68, 70], and in some studies decreased [23•]. This decrease temporally mirrors increasing urbanization of the population and decreasing insect populations. Mortality studies show that they still contribute significantly to fatal anaphylaxis cases—with a large proportion occurring out of hospital [30]. Typically, peak incidence of fatal episodes occurs in men middle aged or older. Fatality rates have not been increasing; however, prompt recognition by first responders and availability out of hospital are factors that could improve outcomes.

Conclusions

Anaphylaxis is a clinical diagnostic, with a clinical syndrome which probably represents a variety of different disease entities with different endotypes and phenotypes having a common end effector. There is no reference standard laboratory test to aid diagnosis, and so epidemiological data is based on clinical diagnosis, medical coding systems and expert opinion. Recent changes to ICD coding systems and definitions will undoubtedly alter the sensitivity for diagnosis and alter estimations of incidence and prevalence, which will have to be taken into account when comparing time periods pre-coding changes. Further research is needed in biomarkers to establish a more useful diagnostic test to confirm suspected cases.

Despite the difficulties in studying the epidemiology of anaphylaxis, the incidence appears to be increasing, in FIA in children and DIA in older adults. Mortality does not seem to have risen as quickly as incidence, which hopefully reflects early diagnosis and treatment as encouraged by the wide reaching diagnostic criteria that have been in use for little more than the last decade.

Author contributions

Both authors contributed to the manuscript conception and literature review. Data analysis was performed by Merlin Ranald McMillan. The first draft of the manuscript was written by Merlin Ranald McMillan, and both authors commented on previous versions of the manuscript. Both authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest

Merlin McMillan and Mário Morais-Almeida declare that they have no conflicts of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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